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TITLE: Topical Treatment of Cutaneous Leishmaniasis W/ WR279396 Phase II Study

PRINCIPAL INVESTIGATOR: Pierre Buffet, M.D., Ph.D.
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CONTRACTING ORGANIZATION: Centre De Recherche Clinique De Institut
Paris, France

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14. ABSTRACT

A second phase 2 clinical study was performed in the Tunisian site to determine: (a) the efficacy and safety of WR279396 administered once a day for 20 days vs twice a day for 20 days; (b) if WR279396 applied under a polyurethane occlusive bandage (Tegaderm™) is more active than application of the drug without occlusion; and (c) the extend of parasite load reduction after a daily application of Wr279396. The study started in January 06 and terminated in February 07. Forty eight (48) patients were included. The preliminary results confirmed the efficacy of the WR279396 in the treatment of the Old World CL. During this reporting period, a two Phase III studies in Old World (Tunis)) and in New World(French Guyana) are being planned.

15. SUBJECT TERMS
No subject terms provided.

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STUDY INVESTIGATORS

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INTRODUCTION

Although the efficacy of WR279396 has been well shown in the 1st Phase II study, 94% in WR group compared with 71% in placebo group, some major questions remained: Can we treat once a day for 20 days instead of twice a day for 20 days? Is occlusion essential? Does the application of WR279396 (once daily) sufficient to significantly decrease the parasite load in the lesions and show cure? In order to answer these questions a 2nd Phase II study was performed. The answers to these questions helped in the design of the pivotal Phase III study to support regulatory approval of this drug.

"*Topical Treatment of Old World Cutaneous Leishmaniasis with WR279396: Efficacy and tolerance of a regimen using an occlusive polyurethane dressing*" (HSRRB Log # A-9768.2) study was conducted from January 2006 to February 2007, in Tunisian site with the lawful and the logistic support, as well as the clinical and financial coordination of the Institut Pasteur of Paris. A total of 48 patients were included, 24 in occluded group and 24 in non-occluded group, 45 completed the study.

PURPOSES

- To determine if the administration of WR279396 once-a-day for 20 days is as effective as twice a day for 20 days when compared to the results from 1st Phase II study.
- To determine whether WR279396 with occlusion (a polyurethane dressing) is more effective than WR279396 without occlusion.

Extensive objective and subjective local tolerance data will also be captured during this trial, as well as surrogate markers (parasite loads) that may also help to determine the optimal number and duration of treatments.

SUBJECT POPULATION

The target study population is male and female patients in Sidi Bouzid area (Tunisia), 15 to 75 years old, who are parasitologicaly confirmed to have cutaneous leishmaniasis obtained in Tunisia.

TABLE 1: Subject Demographics For Protocol Log No. A-9768.2

Subject screened N°	Subject enrolled N°	Age	Gender
W001	002	21	Female
W002	001	47	Female
W004	003	38	Male
W006	004	16	Female
W007	005	15	Female
W009	006	20	Male
W010	007	50	Male
W012	008	17	Female
W013	009	20	Male
W014	010	50	Male
W021	011	16	Female
W023	012	17	Male
W024	013	15	Female
W025	014	16	Male
W029	015	57	Female
W030	016	42	Male
W031	017	38	Male
W032	018	19	Female
W033	019	53	Male

W035	020	75	Female
W037	021	75	Male
W040	022	17	Female
W043	023	40	Female
W044	024	40	Female
W045	025	38	Male
W047	026	16	Male
W048	027	75	Male
W050	028	20	Male
W051	029	24	Female
W055	030	27	Male
W056	031	53	Female
W057	032	21	Male
W058	033	73	Male
W060	038	35	Male
W061	039	40	Male
W062	034	54	Female
W063	035	31	Female
W064	036	64	Female
W065	037	50	Female
W066	040	16	Female
W067	041	20	Female
W068	042	40	Male
W069	043	51	Female
W070	044	72	Male
W071	045	55	Female
W072	046	65	Male
W073	047	48	Female
W074	048	47	Male

TABLE 2. Total Number Of Subjects

Originally planned for Study	40
Site:	Tunisia:
Screened:	74
Total of enrolled as per Amendment 2	48
By Group:	
Occlusion:	24
Non occlusion:	24
Dropped for any reason*:	3

*1 withdrawal treatment at D7, 1 and 1 used IL-Glucantime at D22.

STATUS

The 2nd Phase 2 study was performed from January 2006 to February 2007. Forty-eight subjects with Old World cutaneous leishmaniasis were randomly allocated to receive topical WR279396 treatment, once a day with occlusion (24 subjects) or without occlusion (24 subjects) for 20 days. Forty-five subjects completed the study: One subject withdrawal treatment at D7, and one used intralesional Glucantime at D22.
Efficacy was evaluated in terms of the number of lesions cured at 30 days after the end of therapy (i.e., 50 days from the start of treatment) and the number of relapses during 3 months observation. Toxicity was evaluated by local adverse reactions and by clinical and laboratory signs of systemic events.

Organization Pivotal phase 3:

- Preparation of documents, protocol, IC, CRF, SOPs.
- Coordination with the different investigational sites Tunis and the Parasitology Laboratory conducting the parasite load analysis, Paris, France

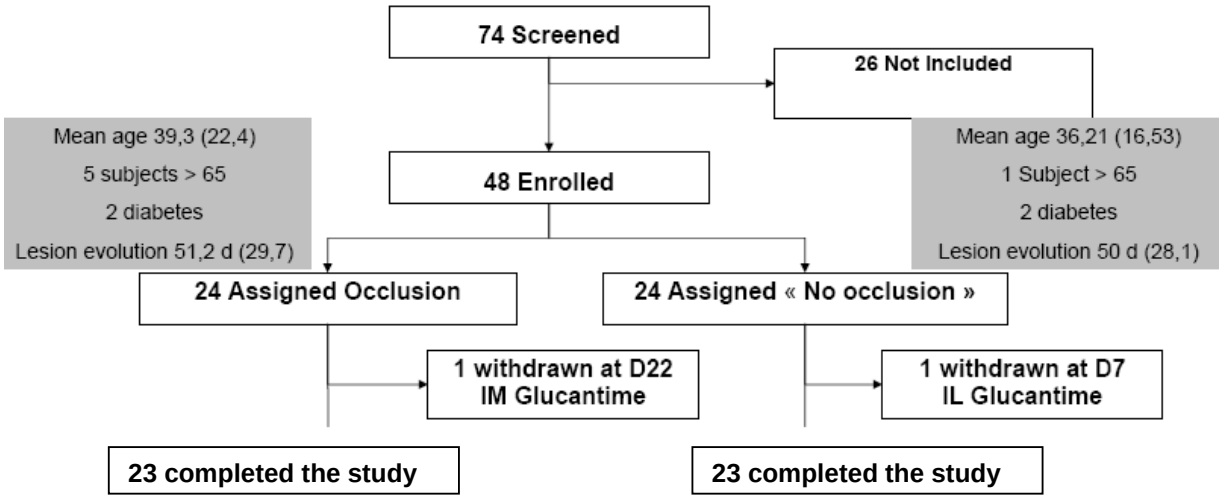
Pre-initiation meeting (Appendix 4) was performed in Tunis, July 2007. The pivotal phase 3 was presented to the General Director of the Pasteur Institute of Tunis who expressed his support to the new project.

The Study documents were revised and approved by the participants.

The Quality Assistance Team visited the Sidi Bouzid site.

The members of the Tunisian team attended a cGCP course.

STUDY RESULTS FOR A-9768.2



43 / 48 cured (89,6% ITT, 93,5% per-protocol)

PARASITE LOAD RESULTS

OCCLUDED

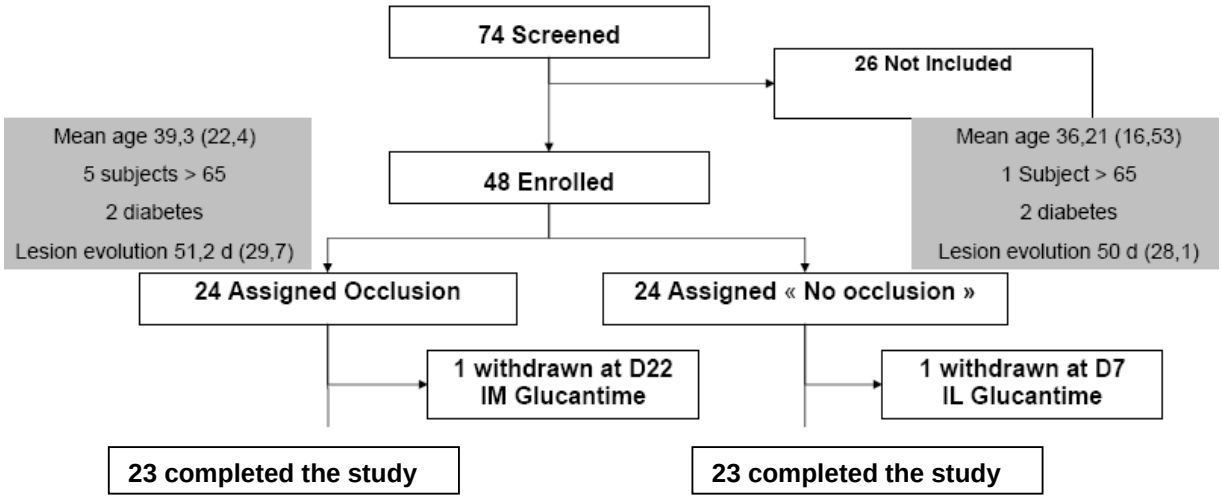
Screening n°	Sub n°		Parasites /gm D0	Parasites /gm D10
W002	001	S	QS not met*	
		D		
W004	003	S		
		D		
W006	004	S		
		D		
W010	007	S	45255	25
		D	18286	11
W012	008	S	108612	172
		D	153600	33
W013	009	S	261	585
		D	808	62
W021	011	S	7257	857
		D	11519	65
W023	012	S	1512	2540
		D	733	21
W024	013	S	11519	560
		D	1263	79
W025	014	S	529	59
		D	2005	21

NON OCCLUDED

Screening n°	Sub n°		Parasites /gm D0	Parasites /gm D10
W001	002	S	QS not met	
		D		
W007	005	S	2667	20
		D	8000	20
W009	006	S	120680	38
		D	241359	223
W014	010	S		Withdrawn
		D		
W029	015	S	11314	76
		D	4682	19
W030	016	S	2824	48
		D	9600	16
W031	017	S	236	771
		D	1333	39
W033	019	S	11806	188
		D	6171	300
W035	020	S	21333	429
		D	2087	236
W040	22	S	2137043	2951
		D	789903	4000

*** Quality Standards not met due to non-adapted inverted microscope (Amendment N° 2)**

STUDY RESULTS FOR A-9768.2



43 / 48 cured (89,6% ITT, 93,5% per-protocol)

W071	045	S	1333	120
		D	250	120
W072	046	S	1697	101
		D	16456	30

W073	047	S	No data	273
		D		157
W074	043	S	No data	771
		D		500

Parasite Load Mean

	Occluded (Tegaderm)		Non occluded (Handsaplast)	
	D0	**D10**	**D0**	**D10**
Superficial	**10 954**	**367**	**232 088**	**1004**
	3.32	**2.2**	**4.19**	**2.46**
Deep	**15 474**	**59**	**72 168**	**446**
	3.4	**1.66**	**4.01**	**2.13**

Pooled data

	D0	D10
Parasite Load Mean (SD)	**78 812** (313 454)	**458** (904)
Mean Log-transformed values	**3,71** (0,93)	**2,10** (0,66)

Ie, 1.6 Log (parasites/gram) in 10 days (x40 in real values)

ADVERSE EXPERIENCES

No Serious Adverse Events occurred.

One subject presented fever 38.2 and headache, classified as an infectious syndrome from D8 to D19, and treated by aspirin and erythromycin for 10 days. No significant laboratory abnormalities were founded. Four subjects developed a slight increase of creatinine between D10 and D20 but they all returned to normal values during the follow up within one month.

Only minor and expected local reactions were found in 14 subjects, all of short duration, limited to small vesicles around the lesions and required no treatment. There was one case of moderate erythema and edema in the XX group. Pruritus, erythema and mild vesiculation occurred on skin covered by the dressing (Tegaderm) in 6 subjects that required application of low potency topical corticosteroids. Significant improvement was obtained in 2-3 days in all groups??.

SUBJECT DROPOUTS IN ASSOCIATION WITH ADVERSE EVENTS

There were no subjects withdrawn in association with adverse events.

DEATHS

There were no deaths.

CONCLUSION

The preliminary results of the 2nd Phase 2 study confirmed the efficacy of WR279396 in the treatment of Old World Cutaneous Leishmaniasis. Application once daily for 20 days is as effective as twice daily for 20 days. Occlusion with Tegaderm does not appear to improve the clinical response, a simple tape and gauze could be used to keep the lesion clean and prevent removal of the topical.

APENDIX 1

« Trip Notes » Pierre Buffet Institut Pasteur Paris
Tunisia 14th – 16th of May 2006

Protocol : Topical Treatment of Old World Cutaneous Leishmaniasis with WR279396 (paromomycin/gentamicin ointment): Efficacy and tolerance of a regimen using an occlusive polyurethane dressing. IND 50 098

Objectives

1. Perform quality control for Limiting Dilution plates reading and confront to clinical evolution

2. Favour coordination between different approaches for parasite loads evaluation

3. Help Pr. Afif Ben Salah to lighten his logistical constraints (Team incentives, miscellanous expenses) Meet Pr. Abdelhadim Ben Abdelhadim director of Institut Pasteur in Tunis in that perspective

4. Prepare Meetings (WRAIR USAMDA TEVA IPT IPP DNDI WHO) in Paris in June

<u>Sunday 2006-05-14</u>

10:35 – 11:15	Av de saint Mandé, Paris – Paris CDG Airport
12:40 – 15:05	CDG Airport – Tunis Carthage Airport
15:40 – 16:00	Car rental
16:30 – 19:30	Tunis Carthage Airport– La Kasbah Hôtel Kairouan
20:30 – 21:30	Trip notes

<u>Monday 2006-05-15</u>

8:00 – 12:00 Prepare June meeting

12:50 Meet with Pr. Ben Salah and Mr. Amor Zaatour

13:00 – 15:00 La Kasbah Hôtel Kairouan – Sidi-Bouzid site
IP Tunis car. Prepare meeting with Pr. Ben Abdelhadim

15:00 – 17:00 Blind parallel reading of plates with Amor Zaatour
Plates seeded on 7th of May 2006
   a. One quality control plate
   b. D10 plates from patients W47, W48, W50, W51

Results :

a. All wells from 4 plates from patients contaminated. 100% agreement between readers
b. For the quality control plate : agreement upon 91/96 wells. AZ reported as positive 3 wells that were negative according to PB

(wells 7-9, 8-11 and 8-12), and reported as negative 2 wells that were positive according to PB. So 94.8% agreement If this plate would have determined a parasite load the difference between parasite loads according to each reader would have been 0.1 Log.

c. When both readers went back to discrepant wells,
    a. PB found mobile promastigotes with typical flagellum in the wells he reported as positive (1 per well),
    b. AZ found suggestive shapes but without typical movement or flagellum in the wells he reported as positive.
    c. The diagonal pattern from PB reading was closer to the theorically expected one.

Comments:
AZ reading displays a very high sensitivity with rare cases of possible over-sensitivity (3 potential "false" positive). Reading of that particular plate was difficult because read only once 7 days after seeding.
In summary: This incomplete QC provides a reasonable validation of cohorts 2 to 7, but we need one more QC with uncontaminated plates from patients (September).

17:30 – 19:50 To allow confrontation to last clinical results checked patients pictures and D50 outcome with ABS. Two patients with complex aspect at D50. One patient with thick squamous plaque of the leg. One patient with 2 red peripheral nodules. Advise given : For patient with plaque : Follow SOP i.e., apply Emla cream then remove the crust to assess reepithelialization under the crust (if required after a needle infiltration of the lesion with xylocaine). If the ulceration is still present : measure ulceration and proceed as per protocol. For the patient with nodule. Measure nodule Is there a new ulceration on the nodule ? Perform smear and look for stainable parasites. If ulceration and parasites present = relapse.

19:50 – 20 :45 Visiting patients at the El Mnara and Nasr Allah sites.

20:45 – 22:20 Nasr-Allah site – La Kasbah Hotel Kairouan

Tuesday 2006-05-16

07:00 – 08-55 La Kasbah Hotel Kairouan - Institut Pasteur Tunis Rent car

09:05 – 09 :30 Meeting with Pr. Ben Abdelhadim Director of Pasteur Institute Tunis

	Presentation of the project by Pr. Ben Salah. Presentation of Meetings in June by PB. Results of site visit: recruitment 28 patients, quality of data for parasite loads measurements OK. Need support to the field team. Institut Pasteur Paris can help by transferring the funds fast but can not control money distribution in Tunisia. The transfer of money will be performed very soon along with a letter of explanation.
09:40 – 10:55	Meeting with Pr. K Dellagi, H Louzir, A Ben Salah, M Mokni, Mrs. Aurélie X, to share information on the different approaches used to determine the parasite loads in the dermis. Presentation of the project by ABS. Presentation of situation on Limiting dilution (including last QC) by PB. Presentation of methods and results of real-time quantitative PCR by Mrs. Aurélie X and Pr. H Louzir.
11:00 – 14:40	Working session with Amor Zaatour : double reading of all “Biopsy forms”, correction of discrepancies between paper forms and Excell sheets already filled by PB from forms previously faxed to Paris by AZ. Comments and clarifications on annotations from AZ. Signature and date on all forms (except cohort 1, because quality insufficient for analysis)
16:00 – 17:30	Working session with ABS. ABS provides a Table summarizing recent miscellanous expenses with written justifications, for PB to give to Isabelle Cailleau for reimbursement. Preparation of a letter to Pr. Ben Abdelhadim that will accompany the money transfer from IPP to IPT (19 000 US$). Decision upon Phase 2 results communication at the DNDi meeting in Paris. PB prepares the 2-pager. ABS will perform the 3-slides communication.
17:30 – 18:00	IP Tunis – Tunis Carthage airport.
18:00 – 18:15	Give the rent car back.
18:20 – 18:40	Registration
18:40 – 19:00	Finalization of letter to Pr. Ben Abdelhadim. E-mail to Isabelle Cailleau for money transfer order.
20:30 – 21:30	Trip notes

Annexes :

Pending actions

a. Give reimbursement papers from ABS to Isabelle Cailleau (PB)
b. Mail copies of double-checked Biopsy Forms to PB (AZ)
c. Write 2 pager for June Meeting (PB)
d. Prepare 3 slides for June Meeting (ABS)
e. Send updated weekly report to team ASAP (including toxicity data) (ABS)
f. Send results (electronic) of quantitative PCR to team. (HL)
g. Send results (electronic) of limiting dilutions to team (PB)

MONDAY 25-sept-06	**AM**	Meetings with Comptroller, P. Buffet, and G. Morizot to discuss Paris-Tunis coordination.	Meeting Parasite load analysis/validation
	PM	**14:00** Meeting with I. Caillau: Funding transfers to Tunis: how do these occur?	C. Ottone, A-S. Lequern P. Buffet, G. Morizot
		Timetable and scope for new Cooperative agreements	Aminoglycosides load/validation **At Clinical Research Laboratory**
TUESDAY 26-sept-06	**AM** **PM**	Travel to Montpellier Visit Pr. Dedet, Isoenzymes Analysis to support Phase 3 Travel to Paris	
WEDNESDAY 27-sept-06	**AM**	Review of Study A-9768.2	
	PM	**14:00** Meeting with Dr Vincent RICHARD – Epidémiologie - Santé Armée **15:30** Meeting with G. Milon and T. Lang	ATU Etudes Van Gogh Finalize Manuscripts

APENDIX 3

Pierre Buffet Institut Pasteur Paris
Trip to Tunisia 8-9 Dec 2006

Protocol : Topical Treatment of Old World Cutaneous Leishmaniasis with WR279396 (paromomycin/gentamicin ointment): Efficacy and tolerance of a regimen using an occlusive polyurethane dressing. IND 50 098

Objectives of the trip:

1. Quality control of plates reading (limiting dilution process for the evaluation of dermal parasite loads)
2. exchange information with Pr. Ben Salah and team on the preliminary results of the ongoing study, in a Phase 3 perspective.

Results

1. Quality control of plates reading (limiting dilution process for the evaluation of dermal parasite loads)

Two plates corresponding to 192 wells were read in parallel the same day by AZ and PB without any communication between readers in the presence of several witnesses. Plates were from patients W068 and W074, both at D10, and had been seeded on 4th and 5th of December. This was a very stringent quality control since (i) plates were read 5 days after seeding when optimal window is 8-10 days post-seeding, (ii) parasite loads are usually lower at D10 than at D0 and promastigotes are harder to distinguish in low dilution wells that contain dermal debris than in "clean" high dilution wells.

There were 15 discrepant wells (7.8%), 13 corresponding to a single promastigote per well. It is then very likely that a few days latter (after multiplication of each single parasite) the discrepancy rate would have been even lower.

Calculation of log transformed last positive dilution gives:

	W068		W074	
	Superficial	Deep	Superficial	Deep
A Zaatour	1,05	0,75	1,5	1,35
P Buffet	1,2	1,65	1,35	1,35

Conclusion : The inter-observer mean error (distance to consensus) was 0,15 Log (0 – 0,45). In a previous analysis variation between D0 and D10 values was 2 Log. Variation between measures from the same observer are probably lower than between observers. The limiting dilution results provided by Amor Zaatour are robust (an exceptional performance). Results from this test signed by AZ/PB will be put in file.

2. Exchange info with Pr. Ben Salah and team on the preliminary results of the ongoing study

a. Global clinical efficacy

Out of 38 patients already seen at D50, 35 cured (1 failure and 1 relapse in occluded group, 1 lost in non occluded => preliminary ITT CCR = 92.1%). Like in the first Phase 2, 33/35 CCR were complete reepithelializations before D50, the 2 others decreased by > 50% at D50 then cured before D80 (one in each group). Evaluation of "day of cure" shows that out of 35 CCR, 31 patients cured before D42. So, for the Phase 3 protocol, D42 is better than D50 for major end-point definition (will probably increase the delta).

b. Efficacy in non-test lesions Are there nodular lesions

18/48 patients had multiple lesions. 5 patients had 2 lesions, 5 had 3, 5 had 4 and 3 had 5 lesions. Eleven of the 42 "non-test" lesions had an ulceration area < 20% of induration area. Two had an ulceration area < 10% of induration area. Most of those "quasi nodular" lesions (25 are "evaluable" today), cured except one in a patient whose test lesion also failed[1]. As in first Phase 2 discrepancy between test lesion evolution and all lesion (i.e., patient) evolution was small. "Quasi" nodular lesions cured as well as widely ulcerated ones.

c. Safety At a glance local tolerance was better than in first Phase 2 (likely due to once a day application). There was a 5 – 15% of mild to moderate acute vesicular reaction on surrounding skin (well balanced between groups).

d. Recently the majority age in Tunisia was change from 20 to 18 years old

e. Dressing : The non occluded regimen was administered under either "sparadrap perforé" or Handsaplast dressing. Handsaplast comes with its own thin gauze, whereas sparadrap perforé was put on the top of a separate gauze. In spite of their small holes, these dressings likely have an occlusive effect. The consequences of this observation are not trivial since - at least until we gather more information about Handsaplat & co – we can no longer assume that our "non-occluded" group corresponds to an application without occlusion. While this likely explains the discrepancy between recent animal results showing a significant effect of occlusion and the absence of clinical and parasitological difference between groups in this bridging study, it has an important (unexpected but positive) consequence on Phase 3 design : application during Phase 3 should be performed with application of either handsaplast ou sparadrap on top of the lesion. It might be useful to test this dressing in mice. Pr. Ben Salah a,d team will make several îsture of the dressing before and after removal at D20

[1] This patients(75 year-old)had a very long very large lesions that cured but relapsed. Then did not cure after intralesional glucantime but eventually improved after IM Glucantime (follow-up still ongoing). (Pr. Ben Salah and team will gather all therapeutic info on this patient, including speciation ie., check if it is not L. tropica).

APENDIX 4

Trip Report - Gloria Morizot Institut Pasteur Paris

INSTITUT PASTEUR TUNIS 08-13 July 2007

Project: Topical Treatment of Cutaneous Leishmaniasis with WR279396.

Phase 3 Study: pre-initiation meeting.

Presents: Philip L. Smith, Ph.D.
Product Manager
USAMMDA

Afif Ben Salah
Principal Investigato

Gloria Morizot
Study Coordinator

Shirley Roach
Monitor

Louis Jasper
Brian Roberts
Heidi Moynihan
Sharon Maloid
Quality Assistance Team

Subinvestigators:
Nathalie Messaoud
Evelyne Guedri
Adel Gharbi
Sadok Cliff
Nabil Haj Hmida
Yamel Eddine Agoubi
Amor Zaatour

Objectives:

1- Present and discuss with the study team the protocol of phase 3
2- Present and discuss the case Report Form
3- Finalize, explain and discuss the Standard procedures (SSPs) with investigators
4- Check the degree of completeness of the study file
5- Undertake a GCP training
6- Discuss and ensure compliance of FDA regulations in the eCRF with computing team of the Department of Epidemiology of Institut Pasteur
7- Close the bridging study

Sunday 8th of July

14:30 Fly Paris – Tunis

17:00 Hôtel Les Ambassadeurs

Monday 9th of July

9:30h – 11h: Meeting with General Director of Institut Pasteur Tunis

11h – Departure of the Sidi Bouzid working group (B. Roberts, S. Maloid, A. Zaatour)

11h – 13h30: Historical update of the project (Philip Smith)

Lunch Break

14:30h- 17h: Protocol presentation (Afif Ben Salah/ Philip Smith)

Tuesday 10th of July

9h-10h30: Protocol discussion session 1 (all participants)

10h30- 11h: Coffee Break

11h –13h30: Protocol discussion session 2 (all participants)

Lunch Break

14h30 –17h: Case Report form discussion (Shirly, Gloria, Adel and Sadok)

Wednesday 11th of July

9h-10h30: Consent Form discussion session 1 (all participants)

10h30- 11h: Coffee Break

11h –13h30: Consent Form and Assent Form discussion session 2 (all participants)

Lunch Break

15h –17h: Case Report and Source documents discussion (Shirly, Gloria and Adel)

Thursday 12th of July

9h – 11h: Workshop on SSPs and study file (Shirly, Gloria and Adel)

11h –13h30: Close out of Bridging study (Shirly, Gloria and Adel)

Lunch Break

15h – 17h GCP course session 1 (Gloria)

Friday 13th of July

10:30 Fly Tunis - Paris